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Craig J. Arnold, Esq.
Amster, Rothstein & Ebenstein
90 Park Avenue
New York, NY 10016

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,170	IAVARONE ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed July 16, 2004 in response to the Office Action of May 18, 2004 is acknowledged and has been entered. Claims 1-18 are pending in the application and Claims 1-9, 16-18 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 10-15 are currently under prosecution.

2. The response to the restriction requirement of May 18, 2004 has been received. Applicant has elected Group 3, claims 10-15 for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

3. Upon review and reconsideration Restriction to one of the following inventions is required under 35 U.S.C. § 121:

4. Claims 10 links inventions 10A and 10B. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 10. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re*

Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Group 10A Claims 10-15 are drawn to a method for assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising *in vitro* assay of a diagnostic sample of the subject for Id2 protein expression, classified in Class 435, subclasses 4 and 7.1.

Group 10B Claims 10-15 are drawn to a method for assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising *in vivo* assay of a diagnostic sample of the subject for Id2 protein expression, classified in Class 435, subclasses 4 and 7.1.

5. The inventions are distinct, each from the other because of the following reasons:

Inventions 10A-10B are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of

inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

9. A telephone interview with Mr. E. Glendoff resulted in Applicant's election of Group 10A, drawn to *in vitro* assay, on September 24, 2004. Affirmation of this election must be submitted with the response to this Office Action.

Specification

10. The specification on page 1 should be amended to reflect the status of the parent application.

11. It is noted for Applicant's convenience that paragraphs 0126 and 0127 of the specification appear to be identical.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and

shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 10-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising assaying for Id2 expression wherein detection of Id2 expression in said sample is indicative of a need to continue therapy and an absence of said expression is indicative of successful therapy, wherein said neoplasm is neuroblastoma, wherein the diagnostic sample is assayed with an agent reactive with Id2, wherein said agent is labeled, wherein said agent is an antibody, wherein said antibody is labeled.

The specification teaches that prior to the present invention, it was not known that Id2 protein is highly expressed in cells of neuroblastomas and other solid pediatric tumors and it was also not known that Id2 mediates signaling by Myc oncoproteins, such that inhibition of Id2 in solid pediatric tumors has an antiproliferative effect (p. 4, para 0013). The present invention is based upon the discovery that Id2 is expressed at significantly high levels in tumors of subjects who have neuroblastoma and the discovery that inhibition of Id2 interrupts the Myc-Id2 transcription pathway and has an antiproliferative effect. These discoveries have broad implications in the diagnosis, monitoring, and treatment of neuroblastomas and other pediatric neoplasms (para 0014, bridging pages 4-5).

The specification exemplifies the expression of Id2, as determined by immunohistochemical staining in primary human neuroblastomas from patients with different tumor stages (page 8, para's 0028-0029), wherein a highly significant correlation between N-Myc and Id2 expression is found in neuroblastoma. The specification further depicts Id2 and N-Myc immunohistochemical analysis of serial tumor sections wherein in the majority of cells in a stage 1 neuroblastoma, N-Myc and Id2 are absent, and in a stage 4 neuroblastoma, high levels of both N-myc and Id2 are detected . The specification further teaches that levels of Id2 expression may be assessed while the patient is undergoing treatment or after treatment for a pediatric neoplasm and wherein Id2 expression continues to be detected, a physician **may** (emphasis added) in choose to continue with the treatment, wherein Id2 expression levels decrease through successive assessments, it **may** (emphasis added) be an indication that the treatment for the pediatric neoplasm is working and wherein levels of Id2 do not rapidly decrease through successive treatments, it **may** (emphasis added) be an indication that the treatment is not working. Where Id2 expression is no longer detected in an assayed diagnostic sample, a physician **may** (emphasis added) conclude that the treatment for a pediatric neoplasm has been successful and that such treatment may cease (para 0055, pages 18-19). In addition, assessment of levels of Id2 **may** (emphasis added) provide a convenient way to conduct follow-ups of patients with pediatric neoplasm (p. 19, para 0056). The specification states that the results disclosed provide compelling evidence in favor of Id2 as a physiologically-relevant, direct target of Myc transcription factors (p. 43, para 0124). The specification exemplifies the analysis of Id2 present in 32 primary neuroblastomas taken from patients with different clinical stages of disease,

wherein the inventors found a highly significant association between expression of Id2 and unfavorable clinical stage and found that the percentage of tumor cells expressing Id2 is significantly higher in most advanced unfavorable stages of neuroblastoma (p. 43, para 0125). The inventors found an essentially perfect correlation between Id2 expression and N-Myc expression in primary neuroblastomas (p. 43, para 0126).

One cannot extrapolate the teaching of the specification to the enablement of the claims because subsequent to the filing of the instant application four different research groups have called into question, the findings and conclusions presented in the instant application and apparently published-in-part by Lasorella et al in Cancer Research, 2002, 62:301-305. In particular, Lasorella et al published Figure 15 of the instant application (see Figure 2 of the reference) to support the argument that Id2 is critical for cellular proliferation and is the oncogenic effector of N-Myc in human neuroblastoma. It is noted that neither the Cancer Research reference nor the instant application discloses a normal control for comparison of expression levels of Id2 protein. The reference teaches that the unique feature of assaying Id2 in neuroblastoma is that its expression integrates the effects of N-myc activation and possibly other upstream signals to overcome the crucial tumor suppressor function of the Rb pathway (p. 306). The Cancer Research reference concludes that the observations suggest that Id2 makes a major contribution to the inappropriate cell proliferation that results from loss of the Myc-Id2 pathway negative control of Rb upon Id2 in tumors (p. 306, last paragraph). However, Sato et al (EJSO, 2003, 29:284-287) specifically teach the results of their investigations suggest that Id2 does not play a major role in the oncogenesis or development of neuroblastoma (p. 286, col 2). Assay of Id2 mRNA expression revealed that Id2 mRNA is expressed

in all primary neuroblastoma samples, irrespective of N-myc mRNA expression and is also expressed in the normal ganglion cells at comparable levels (para bridging pages 284-285 and p. 286, col 2). Sato et al further teach that mRNA expression of Id2 did not correlate with the patient's age, gender, tumor stage, DNA ploidy pattern or mRNA expression of N-myc in the resected samples of neuroblastoma. Sato et al have shown that Id2 continues to be expressed in the differentiated adult ganglion and again state that it is unlikely that Id2 is related to the oncogenesis of neuroblastoma. Sato et al specifically state that their results suggest that N-myc does not control Id2 mRNA expression, "in contradiction to the suggestion made by Lasorella et al, 2000, Nature, 407:592-598". Sato et al further state that although more clinical samples with N-myc gene amplification need to be studied, expression of Id2 in the normal ganglion suggests that Id2 does not play an important role in the oncogenesis of neuroblastoma (para bridging pages 286-287). Given the disclosed expression of mRNA in both normal ganglion and neuroblastoma samples, given the clear statement, contrary to that of the instant specification, that Id2 expression is not correlated to N-myc expression and that it is unlikely that N-myc controls Id2 mRNA expression, as stated by the instant inventors, given the clear statement that it is unlikely that Id2 is related to oncogenesis of neuroblastoma, given the lack of normal control data from normal ganglion, even though the Sato et al data is drawn to mRNA, rather than protein expression, given the lack of differential in mRNA expression in normal ganglion and neuroblastoma cells, it is not possible to predict whether or not there is, in fact, a differential expression of Id2 protein in neuroblastoma tumors compared to appropriate normal controls. Thus it cannot be predicted that the invention will function as claimed in the absence of a demonstration of differential expression of

Id2 protein between primary neuroblastoma samples and appropriate normal controls.

Further, Vandesompele et al (Oncogene, 2003, 22:456-460) point to what they call "the remarkable differences between the present and published data (p. 460)". Specifically, the authors state that because their initial results contrasted with the reported data of Lasorella et al, 2000, 2002, (*Supra)* the decision was made to reinvestigate the potential link between N-Myc and Id2 expression in neuroblastoma by mRNA and protein analysis of six cell lines analyzed by Lasorella et al. Upon repetition of cell line and primary neuroblastoma studies, it was found that there was no correlation between Id2 and N-myc expression in primary neuroblastoma specimens (see p. 456, col 2). No apparent correlation between N-myc and Id2 expression was found at either the mRNA or protein levels (p. 458). The authors state that "These data, obtained in two independent laboratories challenge the previously proposed Id2-N-Myc relation (see abstract). From a clinical perspective, the most important finding by Lasorella et al, 2002, is the association between high Id2 protein immunoreactivity and poor prognosis in neuroblastoma specimens. To test if there is a similar correlation at the mRNA level, mRNA was assessed from 27 neuroblastoma primary tumors. No prognostic value was found for mRNA expression of Id2 in neuroblastoma (para briding pages 459-460). The authors conclude that Id2 and N-myc expression do not correlate in neuroblastoma tumors. No *in vivo* binding of N-myc to the Id2 promoter has been shown and the data strongly suggest that N-myc is not promoting Id2 expression in neuroblastoma. The authors then state that their conclusions are based on mRNA levels while Lasorella et al, 2002 have analyzed Id2 protein levels. To reconcile these observations, one would have to assume a

post-transcriptional regulation of Id2. However, in such case, the mechanisms regulating the Id2 protein levels must be independent of N-myc expression. Thus further studies are needed to clarify the reasons for the remarkable differences between the present and published data (p. 460).

Wang et al (Cancer Research, 2003, 1631-1635) specifically teach that Id2 expression is not associated with N-myc amplification or expression in human neuroblastomas. Northern blotting of neuroblastoma-derived cell lines showed Id2 to be differentially expressed with no apparent correlation to N-myc gene amplification status (p. 1632, col 2), Western blotting confirmed that there is no association between N-myc amplification and Id2 protein expression in the same cell lines (see Figure 2A and Figure 2D, page 1633). Wang et al explicitly state that the data clearly demonstrate no association between N-myc amplification status and Id2 mRNA expression or protein expression (p. 1634, col 2). Wang at al, like Vandesompele et al point out that their studies were done on primary neuroblastoma mRNA and that the only protein studies were done with cell lines (known to be less than satisfactory for providing a nexus between molecular biological events in the *in vivo* environment). They speculate, like Vandesompele et al, that it is possible that post-transcriptional regulation of Id2 is different depending on N-myc amplification status and that an immunohistochemical study of Id2 protein expression could have provided different results, but "this seems unlikely based on our cell line data showing no evidence for differential Id2 expression by Western blotting". It is noted that Wang et al cite Lasorella 2000 and 2002, *Supra* as the source of information drawn to the nexus between Id2 and N-myc.

Finally, if specifically teach that they assessed the requirement for Id2 in mediating Myc-induced papilloma formation in skin and demonstrated that Id2 has no discernible impact on any measurable attribute of Myc function or on the timing or extent of eventual tumor formation. They conclude in the abstract that "our data argue against any essential role for Id2 in mediating Myc action *in vivo*." (see abstract). "Despite the published evidence that Id2 is a pivotal proliferative effector of Myc" (Lasorella et al, 2000 and 2002, *Supra* are cited here) ….. "we found that deletion of the Id2 gene has no detectable influence on the extent or kinetics of the complex neoplastic phenotype elicited by Myc in skin" (see p. 3088, para bridging cols 1 and 2). Murphy et al state that the initial report suggesting a close correlation between N-Myc amplification and Id2 expression in neuroblastoma has recently been called into question (p. 2089, col 1). Murphy concludes that careful analysis of induced epidermal neoplasm throughout its progression revealed no obvious phenotypic deficit ascribable to the absence of Id2 expression. The rate and extent of keratinocyte proliferation, delay in keratinocyte differentiation, dermal angiogenesis and eventual papillomatosis elicited by Myc were all identical in the presence of absence of Id2. While it remains possible that Id2 may still mediate critical Myc functions in specific tissues or tumor types, our studies indicate that Id2 is not a universal requirement for any of the diverse aspects of Myc's biological function.

Although the specification teaches that the present invention is based upon the discovery that Id2 is significantly expressed at significantly high levels in tumors of subjects who have neuroblastoma and the discovery that inhibition of Id2 interrupts the Myc-Id2 transcription pathway, it is clear from the teaching in the art that, at the very least, the findings drawn to the putative N-myc/Id2

interaction in proliferative disease, and in particular neuroblastoma, are questioned by those of skill in the art. It is clear that experimentation by four separate groups have demonstrated that that there is no association between Myc and Id2 drawn to cancer etiology and development. Given the clear questions raised as to the accuracy of the hypothesis upon which the invention is based (that is the relationship between Id2 and N-myc), given the clear questions raised as to the role that Id2 plays in oncogenesis, given the known equivalence of mRNA production in both primary neuroblastoma and normal ganglion cells, given the lack of appropriate normal controls, given the teaching that Id2 mRNA does not correlate with tumor stage, given the teaching that Id2 has no effect upon induced epidermal neoplasms, it could not be predicted that the efficacy of therapy to treat a pediatric neoplasm could be determined by assay of a sample for Id2 protein expression.
It is noted that although the claims are drawn to a method for assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm by assay of Id2 protein, in the body of the application there is no exemplification of claimed method and when referring to determining efficacy of treatment, the specification repeatedly makes use of phrases such as Id2 reduction "may be an indication that the treatment .....is working" and the "physician may conclude that the treatment.....has been successful". It is clear that the instantly claimed method is an undeveloped art. It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that

teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

14. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, Claims 10-15 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of assessing the efficacy of therapy to treat a pediatric neoplasm which **prior to treatment** expresses Id2 protein, comprising assaying a diagnostic sample for expression of protein Id2 does not reasonably provide enablement for a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein. This means any and all pediatric neoplasms, regardless of whether or not they

expressed Id2 protein prior to treatment. The specification teaches that Id2 mRNA is overexpressed in neoplastic cells that give rise to pancreatic cancers and that Id2 mRNA expression is prominent in certain leukemias. Prior to the present invention, it was not known that Id2 protein is highly expressed in cells of neuroblastomas and other solid pediatric tumors ((p. 4, para 0013). Further, the present invention is based upon the discovery that Id2 is expressed at significantly high levels in tumors of subjects who have neuroblastoma and these discoveries have broad implications in the diagnosis, monitoring and treatment of neuroblastomas and other pediatric neoplasms (p. 4-5, para 0014).

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims are drawn to assessing the efficacy of any type of therapy for a pediatric neoplasm and thus the claims are in actuality drawn to assay of whether or not that therapy has killed/eliminated all of the tumor cells, resulting in successful therapy wherein that therapy can be stopped. It is not clear from the information in the specification how one would go about determining whether therapy had been successful if the pediatric neoplasm had never expressed Id2. Certainly, the specification makes clear that, for example, not all leukemias express Id2 (p. 4, para 0013). It certainly would not be expected that assay for Id2 in those leukemias, or any neoplasm that did not express Id2, could be successfully assessed for the efficacy of therapy by assaying for Id2 expression. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of

success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

15. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 10-15 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein, wherein detection of Id2 protein expression in the diagnostic sample is indicative of a need to continue therapy, or to discontinue therapy in favor of an alternative therapy does not reasonably provide enablement for a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein **wherein absence of Id2 expression in the diagnostic sample is indicative of successful therapy**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein expression wherein detection of Id2 expression in said sample is indicative of a need to continue therapy and an absence of said expression is indicative of successful therapy, wherein said neoplasm is neuroblastoma, wherein the diagnostic sample is assayed with an agent reactive with Id2, wherein said agent is labeled, wherein said agent is an antibody, wherein said antibody is labeled.

The specification teaches that a diagnostic sample may be tissue, particularly any bone, brain tissue, kidney tissue, muscle tissue, nervous tissue, retinal tissue,

or soft tissue, which may be removed by standard biopsy. In addition, the diagnostic sample may be a bodily fluid, including cerebrospinal fluid, pericardial fluid, peritoneal fluid, saliva, serum, and urine. Furthermore, the diagnostic sample taken from the subject or patient may be, for example, any tissue known to have a pediatric neoplasm, any tissue suspected of having a pediatric neoplasm, or any tissue believed not to have a pediatric neoplasm (p. 13, para 0041). The specification further teaches that because Id2 is generally not expressed in cells of healthy, non-diseased subjects, that is those that do not have a pediatric neoplasm, detection of Id2 expression in a diagnostic sample of a subject is diagnostic of a pediatric neoplasm (p. 13, para 0043).

One cannot extrapolate the teaching of the specification to the scope of the claimed invention because it could not be predicted whether or not a diagnostic sample that tests negative for Id2 protein is a "normal tissue" that is, one that does not usually express Id2, or whether a negative result is due to efficacy of treatment. Further, it is noted that included in the diagnostic samples are a bodily fluid, including cerebrospinal fluid, pericardial fluid, peritoneal fluid, saliva, serum, and urine. However, the specification teaches that Id2 is not expressed on the surface of cells, that is, it is an intracellular protein that is associated with regulation of cell differentiation. There is no evidence in the specification or in the art of record that Id2 is exported from the cell or that it can be used as a marker in bodily fluids in the same way, for example, that CA125 is exported so that its presence in bodily fluids can be used as a marker for the determination of efficacy of treatment. Further, as drawn to any tissue suspected of having a pediatric neoplasm, or any tissue believed not to have a pediatric neoplasm, again, it could not be predicted whether or not a diagnostic sample that tests negative for Id2 protein is a "normal

tissue" that is, one that does not usually express Id2, or whether a negative result is due to efficacy of treatment. In order to be able to predict whether or not the absence of Id2 expression in a diagnostic sample is indicative of successful therapy, it is essential that it be known, prior to the assessment, whether or not the tissue in fact, did express Id2 prior to therapy. Since the specification is clear that normal tissues do not generally express Id2, it is not clear how, in the absence of information regarding the prior Id2 status of a sample whether or not therapy has been successful comprising assaying Id2 protein in said sample. Further complicating the issue of determining successful therapy by assay of Id2 protein is the art recognized alteration in the expression of tumor antigens as neoplasms progress. In particular, it is known that expression of an antigen can be lost during the progression toward metastasis. Although drawn to prostate cancer, the following references are clearly relevant to the instant rejection. For example, Kibel, AS et al, (2000, J Urol, 164(1): 192-6) teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis. Zhau, HE, (1994, J Cell Biochem, Suppl 19: 208-216), teach expression of various biomarkers associated with prostate cancer progression. Zhau et al teach that in prostate cancer, PC-3N35 subclones which are cloned from primary and metastatic sites (lymph node, kidney and bone), show difference in the levels of protein expression of various markers, such as c-erbB, vimentin, ICAM-1, cytokeratin, collagen IV between the parental PC-3N35 clone and its metastatic subclones (p.209 and table 1) and that the subline derived from the metastatic site lymph node has a 12p:17q translocation, whereas the bone-derived subline contains an isochromosome 7q (p.211, first column, first paragraph). Ren, C et al,

(1998, Cancer Res, 58(6): 1285-90), teach a loss of expression of lysyl oxidase mRNA during progression to metastasis. Gingrich, JR et al, (1996, Cancer res, 56(18): 4096-4102) teach a loss of normal E-cadherin expression as primary of of tumors become less differentiated and metastasize.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 10, 12-15 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of assessing the efficacy of therapy **to treat neuroblastoma**, comprising assaying a diagnostic sample for expression of protein Id2 does not reasonably provide enablement for a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for Id2 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of assessing the efficacy of therapy to treat a pediatric neoplasm comprising assaying a diagnostic sample for expression of protein Id2. This means assessing the efficacy of treatment of any pediatric neoplasm. The specification teaches that a neoplasm is defined to mean any new and abnormal growth and includes both malignant and benign tumors that are

either invasive or noninvasive that included within the scope of the invention are the pediatric neoplasms disclosed on page 12 (para 0039, p. 12). The specification further teaches that prior to the present invention, it was not known that Id2 protein is highly expressed in cells of neuroblastomas and other solid pediatric tumors ((p. 4, para 0013). Further, the present invention is based upon the discovery that Id2 is expressed at significantly high levels in tumors of subjects who have neuroblastoma and these discoveries have broad implications in the diagnosis, monitoring and treatment of neuroblastomas and other pediatric neoplasms (p. 4-5, para 0014). The specification makes clear that, for example, not all leukemias express Id2 (p. 4, para 0013).

One cannot extrapolate the teaching of the specification to the scope of the claims because, other than neuroblastoma, there is no demonstration that Id2 is expressed in any of the pediatric neoplasms disclosed. Although the specification repeatedly links neuroblastoma with all other pediatric neoplasms, whether they are malignant or not, it is not clear from the information in the specification why this link is being made. No nexus has been established between neuroblastoma expression of Id2 protein and the expression of Id2 protein in any other pediatric neoplasm. Certainly, although drawn to closely related cell types, not all leukemias express Id2 protein. Thus, in the absence of objective evidence, it cannot be predicted which, or how many of the widely diverse cell types of the claimed pediatric neoplasms would express Id2 so that the invention could function as claimed. As drawn to expression of Id2 in non-malignant neoplasms, the specification teaches that in immunohistochemical analysis of serial neuroblastoma sections it was found that in the majority of cells in stage 1 neuroblastoma, Id2 is absent and that high levels of Id2 were detected in samples from more advanced

stages of neuroblastoma. Given the suggested progression of Id2 expression from stage 1 to stage 4 tumors it would be expected that Id2 would not be expressed in any of the premalignant neoplasms that precede neuroblastoma. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

17. Claims 15-20 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

It is noted that the specification's states that unless otherwise indicated "Id2" includes both Id2 protein and Id2 analogue. As used herein, the Id2 protein has the amino acid sequence set forth in Figure 13, SEQ ID NO:2, and an Id2 analogue is a functional variant of Id2 protein having Id2 biological activity, has 60% or greater amino acid sequence homology with Id2 protein and includes variants of the Id2 protein that have homologous three dimensional conformations. The term Id2 biological activity refers to the activity of a protein or peptide that demonstrates an ability to associated physically with active hypophosphorylated forms of the Rb family proteins and/or an ability to stimulated growth or act as an effector of Myc oncoproteins in neuroblastoma cells (paragraph bridging pages 11-12). Thus, given the recitation of Id2 in the claims and in the absence of other indication, it is assumed for examination purposes that included within the scope of the invention is Id2 analogue as a target for assessing the efficacy of treatment.

Claims 15-20 are drawn to a method for assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising *in vitro* assay of a diagnostic sample for Id2 protein analogue expression. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that □[a] written description of an invention involving a chemical genus, like a description of a chemical species, □requires a precise definition, such as by structure, formula, [or] chemical name,□ of the claimed subject matter sufficient to distinguish it from other materials.□ Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as □vertebrate insulin cDNA□ or □mammalian insulin cDNA□ without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that □naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.□ Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. □A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.□ Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by □show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. □ Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of Id2 protein analogue, per Lilly by structurally describing a representative number of Id2 protein analogue or by describing □structural features common to the members of the genus, which features constitute a substantial portion of the genus.□ Alternatively, per Enzo, the specification can show that the claimed

invention is complete □by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the Id2 protein analogue required to practice the method of the claims in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any Id2 other than SEQ ID NO:2, nor does the specification provide any partial structure of such Id2, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single Id2, SEQ ID NO:2, this does not provide a description of Id2 protein analogue that would satisfy the standard set out in Enzo.

The specification also fails to describe Id2 protein analogue, as defined by the specification, by the test set out in Lilly. The specification describes only a single Id2. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of Id2 protein analogue as defined in the specification that is required to practice the claimed invention. Since the specification fails to adequately describe Id2 protein analogue, it also fails to adequately describe the method claimed. The rejection may be obviated by amending the claims, for example, to specifically recite Id2 protein, SEQ ID NO:2.

18. Claims 12, 13 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

It is noted that an agent that is reactive with Id2 is defined by the specification as including "a protein, polypeptide, peptide, nucleic acid (including DNA or RNA), antibody, Fab fragment, F(ab').sub.2 fragment, molecule, compound, antibiotic, drug, and any combinations thereof." It is further noted that other than antibody that binds to SEQ ID NO:2, no diagnostic reactive agents have been elucidated in terms of structure correlated with function.

Claims 12-13 are drawn to a method for assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising *in vitro* assay of a diagnostic sample for Id2 protein expression wherein the diagnostic sample is assayed using an agent reactive with Id2. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by

> members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A

disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of said agent, per Lilly by structurally describing a representative number of agents or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the agents required to practice the method of the claims in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any agents other than antibody to SEQ ID NO:2, nor does the specification provide any partial structure of such agents, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses the structure of a single agent, an antibody that binds to SEQ ID NO:2, this does not provide a description of said agent that would satisfy the standard set out in Enzo.

The specification also fails to describe agents by the test set out in Lilly. The specification describes only a single agent known to bind to Id2. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of said agent that is required to practice the claimed invention. Since the specification fails to adequately describe said agent, it also fails to adequately describe the method claimed.

19. Claims 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-15 are indefinite because they omit an essential element. The essential element being assay of a sample wherein the treated pediatric neoplasm expresses Id2 prior to treatment for said pediatric neoplasm.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

21. Claims 10-15 are rejected under 35 U.S.C. § 102(e) as being anticipated by US 20020151681.

It is noted that the specification defines a pediatric neoplasm as any neoplasm that expresses Id2 (p. 13, para 0043). Thus, it is assumed for examination purposes that any neoplasm that expresses Id2 is a pediatric neoplasm.

It is noted that Table 1 of US 20020151681 discloses that SEQ ID NO:1547 is SEQ ID NO:Y. SEQ ID NO:1547 comprises a sequence with 94% identity to SEQ ID NO:2, Id2, and therefore is a Id2 protein analogue as defined by the specification.

It is noted that the specification of US 20020151681 defines a variant as "overall closely similar, and, in many regions, identical to the or polypeptide of the present invention". Given the % identity between SEQ ID NO:1547 and SEQ ID NO:2, it is clear that SEQ ID NO:2 is a variant of SEQ ID NO:1547.

The claims are drawn to assessing the efficacy of therapy to treat a pediatric neoplasm in a subject who has undergone or is undergoing treatment for a pediatric neoplasm comprising assaying for Id2 expression wherein detection of Id2 expression in said sample is indicative of a need to continue therapy and an absence of said expression is indicative of successful therapy, wherein said neoplasm is neuroblastoma, wherein the diagnostic sample is assayed with an agent reactive with Id2, wherein said agent is labeled, wherein said agent is an antibody, wherein said antibody is labeled.

US 20020151681 teaches a method of assessing the efficacy of therapy to treat a pediatric neoplasm, comprising assaying for the expression of SEQ ID NO:Y (para 0207), Seq ID NO:1547, wherein the specification teaches a method of the specific destruction of neoplastic cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs (para 0320), wherein monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc. (para 0269), wherein the

specification specifically claims a method of diagnosing a pathological condition based on the presence or amount of expression of a polypeptide of claim 11 (claim 19), wherein claim 11 is drawn to an isolated polypeptide comprising an amino acid sequence at least 95% identical to a full length protein of SEQ ID NO:Y, SEQ ID NO:1547, or a variant of SEQ ID NO:Y, SEQ ID NO:1547 (Claim 11), wherein the protein is assayed using an antibody/labeled antibody wherein techniques include RIA and suitable labels include iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin (para 0265), wherein other diseases that can be similarly treated and detected by polypeptides of the invention include neuroblastoma (para 0539). Although the reference does not specifically state that detection of Id2 expression in the diagnostic sample is indicative of a need to continue therapy to treat the pediatric neoplasm and an absence of Id2 expression in the diagnostic sample is indicative of successful therapy, these limitations are implicit in the clear teaching of a method of assessing the efficacy of therapy. Given the above, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

22. No claims allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 4, 2004